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Volume XVII SEPTEMBER 1956 Number 9

DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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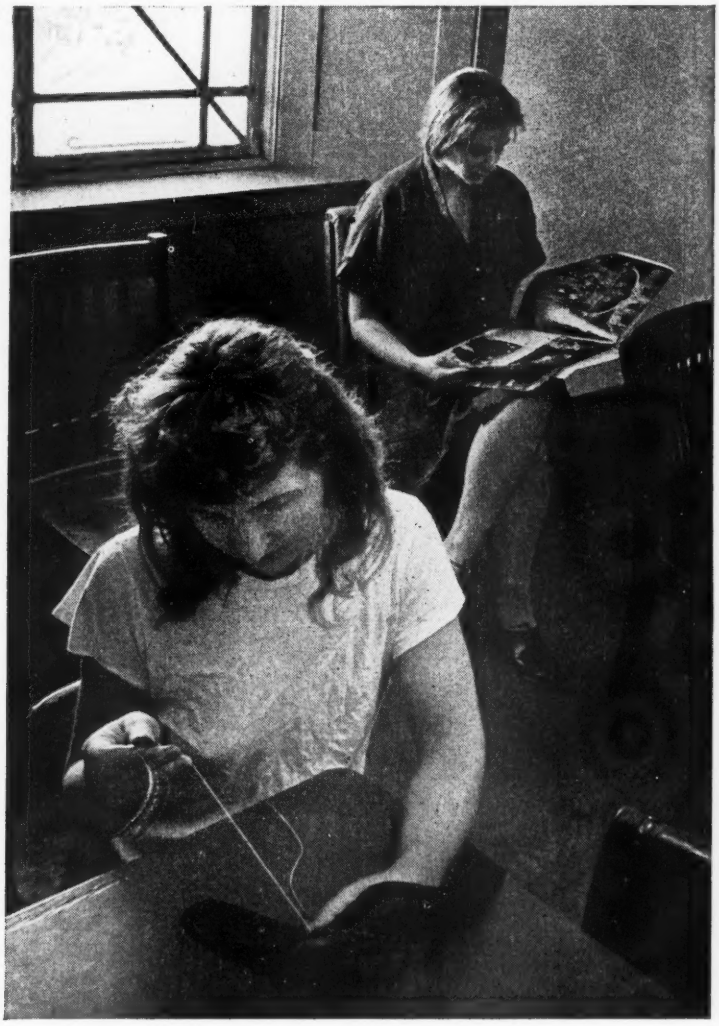

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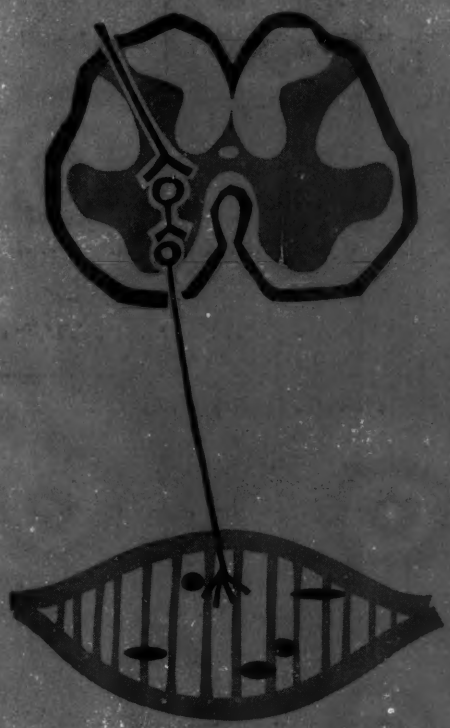

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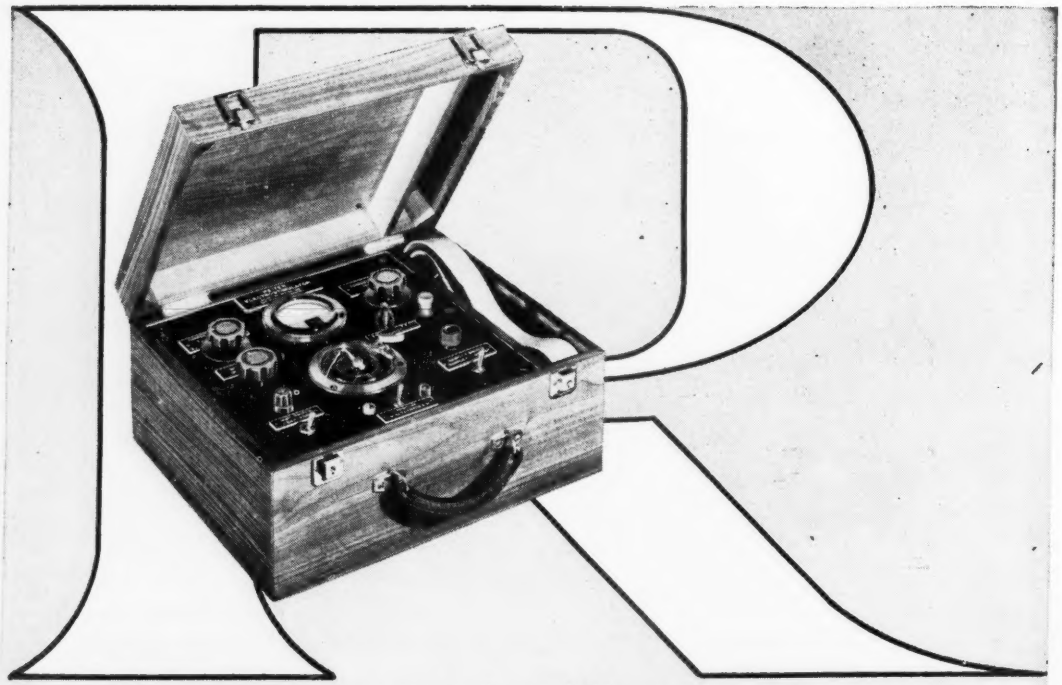

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DISEASES of the Nervous System

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Cerebral Aqueduct Stenosis

(Treatment by Aqueduct-Cisternal Shunt)

JAMES GREENWOOD, JR., M.D., and WILLIAM C. HICKEY, M.D.
Houston, Texas

Complete obstruction to the ventricular system will probably result in death within a period of hours. Partial obstruction, while resulting in increased intracranial pressure, may relieve itself to a certain extent by ventricular enlargement, allowing fluid to pass by a ball valve tumor or by the increased pressure forcing itself past a point of partial obstruction. Stenosis of the aqueduct, whether from scar or from external pressure, may remain partial for a considerable period of time before obstruction becomes complete. The placing of a catheter through a stenosed aqueduct was probably the first shunt procedure. Dandy[1] in 1920 reported two cases for the relief of infant hydrocephalus, but one patient did not survive and the tube was removed in the second case because of severe reaction. Rivarola,[5] a year later, described a similar unsuccessful experience. One of the authors[2] (J.G.) established a shunt in 1941 for aqueduct stenosis with survival of the patient for two years. A second case, still surviving, was reported in 1950.[3] A successful unreported case of Mixter antedated our first case by ten years.[4]

The length of survival, success in relief of hydrocephalus, and simplicity of the procedure would indicate that in some cases at least it has practical application. We feel that rubber is superior to polyethylene except where extremely small caliber is desired. Our cases and that of Mixter would indicate that rubber does maintain its integrity for a great number of years. Case data are tabulated in Table I below.

From the Division of Neurosurgery, Methodist Hospital, and Baylor University College of Medicine.

TABLE I

CEREBRAL AQUEDUCT STENOSIS — AQUEDUCT-CISTERNAL SHUNT

Case	Year	Sex	Age	Lesion	Papilledema	Relief of Hydrocephalus	Survival-Condition
E.B.	1941	F	52	Pineal tumor ?	2 D	Yes	Improvement 18 mos. Expired 2 years
B.M.	1946	M	35	Aqueduct stenosis	3 D	Yes	8 yrs.—employed
L.G.	1948	M	46	Metastatic Ca. cerebellum	No	Yes	5 mos. expired
R.L.	1951	M	2	Meningitis Aqueduct stenosis	No	No	Expired 6 weeks—arachnoiditis
D.B.	1952	F	2 mo.	Arnold Chiari	No	Yes	Expired 14 mos. Pneumonia
B.B.	1952	M	3 mo.	Arnold Chiari	No	No	Expired 2 mos.
J.C.	1952	M	3 wks.	Arnold Chiari	No	Yes	18 mos.—talking
M.	1931	F	17	Arachnoiditis ?	No	Yes	22 years Dr. Mixter's case

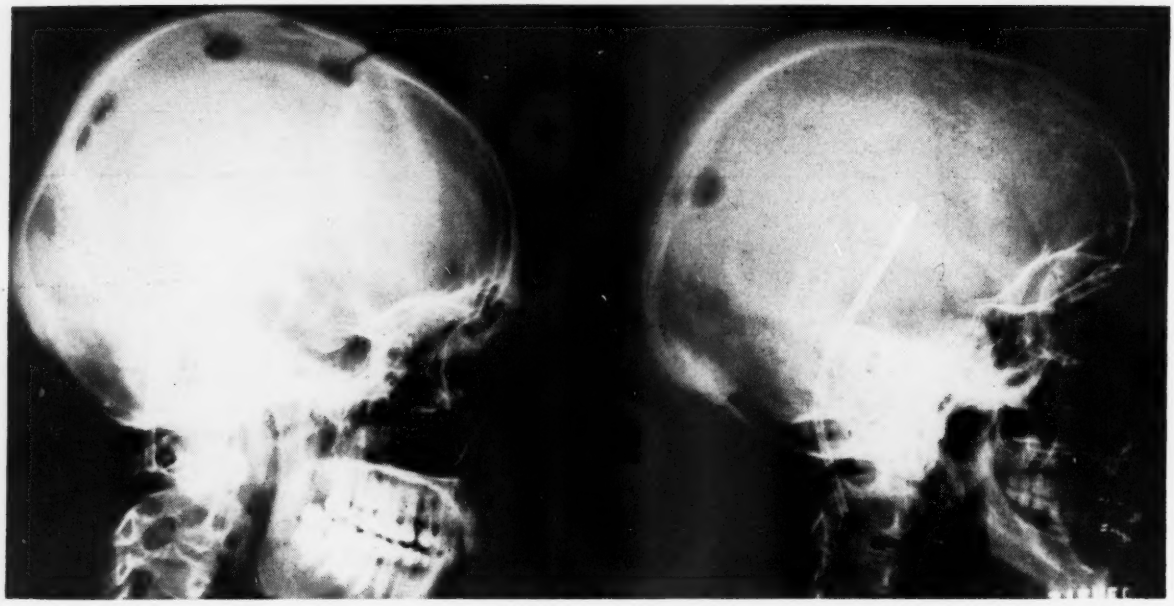

Fig. 1. Left. Aqueduct stenosis by 5th ventricle cyst. Catheter in place now 10 years.

Fig. 1. Right. Relief of 4th ventricle stenosis 5 months. Metastatic carcinoma blocking upper 4th ventricle.

Several cases were considered worthy of reporting in detail.

Case No. 2: B. P. M., a white male, age 35, was admitted to the Methodist Hospital January 12, 1946, because of headaches which had begun five months before and recent stupor and incoordination in walking. There was bilateral papilledema, and ventriculography showed marked dilatation of the lateral and third ventricles and a well-filled fifth ventricle. No oxygen was demonstrated in the aqueduct or fourth ventricle. A midline suboccipital approach was carried out and, after negative cannula exploration of both hemispheres, the fourth ventricle was opened through the vermis, high enough to see the aqueduct. A catheter passed through the aqueduct into the third ventricle against definite resistance was followed by an escape of fluid which immediately stopped once the catheter was withdrawn. The catheter was re-introduced and its lower end cut off at the level of the atlas and fastened in the subarachnoid space with a single silk suture (Fig. 1, left). He was given a course of x-day therapy, slowly improved, and was able to return to work in a filling station eighteen months later. He has been seen at yearly intervals, the last visit being October 5, 1953, at which time he exhibited slight ataxia on walking, a slight tilt of the head to the right, but otherwise was negative neurologically. He has continued to work.

Case No. 3: L. G., a white male, age 46, was admitted on November 28, 1948, in deep stupor, mild Cheyne-Stokes respirations, and a catheter was placed in the right lateral ventricle for emergency decompression. Because of his poor condition, no additional procedure was attempted until twelve days later when a ventriculogram revealed a posterior fossa lesion producing marked internal hydrocephalus. A cystic cerebellar tumor, containing 35 cc. of brownish, cloudy fluid was removed from the left cerebellar hemisphere. Evidence of block re-appeared within seven to ten days and he was re-operated, at which time an additional 10 to 20 cc. of tumor was removed from the upper portion of the cerebellum. Because of the necrotic condition of the surrounding tissue and because of the diagnosis of metastatic carcinoma, a catheter was left in the aqueduct extending up into the third ventricle and fastened in the upper cervical region (Fig. 1, Right). He recovered sufficiently to return home, but was re-admitted to the hospital almost five months later because of facial edema, headaches, and dizziness. He expired within forty-eight hours, and necropsy showed broncho-

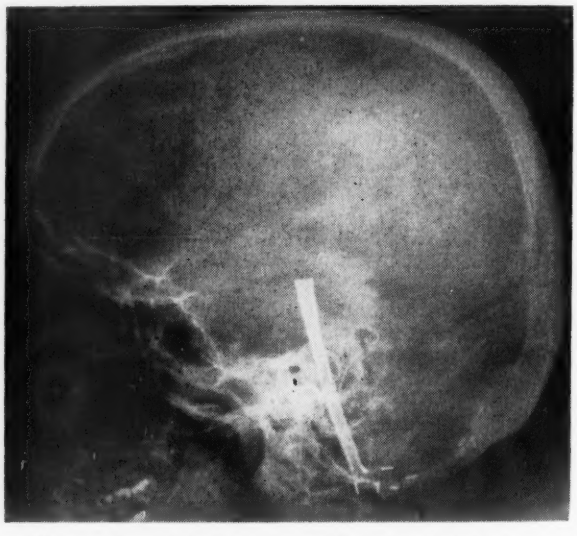

Fig. 2. Dr. Mixter's case (8). Patient living over 16 years.

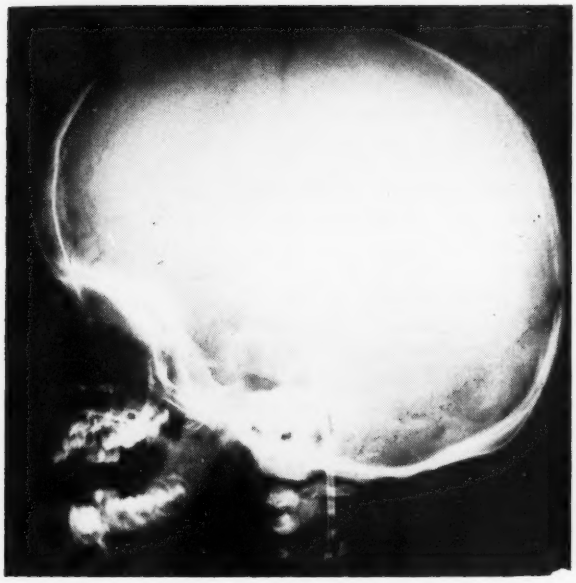

Fig. 3. (Case 7.) Aqueduct stenosis in Arnold-Chiari malformation. 3rd and 4th ventricle very low. Relief of hydrocephalus now for 4 years.

genic carcinoma and recurrence of the left cerebellar metastasis. Detailed microscopic examination of the aqueduct, third and, fourth ventricles showed no microscopic reaction to the rubber catheter.

Case No. 8: (Included through the courtesy of Dr. William J. Mixter.) A white female, age 14, had developed evidence of an obstructive lesion in the cerebellum during childhood. From that time on she had been below par mentally, and when examined in 1931 was extremely unsteady in her gait. Surgery revealed evidence of an adhesive arachnoiditis and obstruction of the aqueduct, which was relieved by passage of a catheter, left in place (Fig. 2). Dr. Mixter felt that the catheter had continued to function, and x-rays taken approximately sixteen years after surgery showed the catheter to be intact in its original position.

Summary and Conclusions

Experiences with the treatment of aqueduct stenosis by aqueduct cisternal shunt have been outlined and the results tabulated in seven cases. An unpublished case of Dr. Mixter's, believed to be the first instance of significant survival following the use of this procedure, has been included.

We believe that the use of an indwelling rubber catheter in the aqueduct is a practical procedure for relief of internal hydrocephalus occurring in stenosis of the aqueduct, block in the region of the fourth ventricle, or its outlets. Relief of symptoms over a long period of time has been obtained and there is reason to feel that there is little reaction to the catheter, either locally or because of distortion of the brain stem. It is obvious that the catheter should not be introduced against any significant resistance because of the possibility of trauma. Its simplicity should in some cases give it preference over other shunt procedures being done at the present time.

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Headaches and Hot Tempers

WILLIAM H. MCCULLAGH, M.D., and WILLIAM INGRAM, JR., M.D.
Jacksonville, Florida

In the private practice of neurology and psychiatry in our vicinity patients with recurrent headaches and emotional outbursts are frequently referred for diagnostic study and management. We have made electroencephalographic tracings in many of these cases and have found dysrhythmias very common. In some, there has been a familial tendency, and in a few, we have been able to get tracings of relatives made for comparison. A high percentage of the parents, or other relatives, show abnormal brain wave patterns. We have also noticed that a very high percentage of patients with migraine type headaches, or emotional outbursts, have a family history which is positive for paroxysmal outbursts of hostility or temper, and there seems to be a definite electroen-

cephalographic relationship between emotional outbursts, some forms of migraine headaches, and the family history. To illustrate, we have the following case histories:

C. D. A. and her mother are instances illustrative of this familiar relationship of headaches, ictal anger and abnormal electroencephalogram. The patient is an eight year old girl who has severe temper tantrums, frequent violent nightmares, is something of a behavior problem, complains infrequently of headaches, and when frustrated is subject to very violent screaming and crying attacks, during which she is unresponsive to environmental influences. Her maternal grandmother has violent temper tantrums, and her mother has migraine and a violent temper, during attacks of which she tears up objects in the household, breaks dishes, stamps her feet and screams, and has amnesia for these events. The grandmother is said to have told the mother that "a violent temper has run in the family for generations." The patient's father also has headaches diagnosed as migraine as had his father and his grandfather. The child's electroencephalogram is grossly abnormal with bursts of slowing to 3-5 cps with spread to all leads and some disorganization. The mother is 43 and her electroencephalogram is also regarded as abnormal with irregularities in voltage and rhythm and the occurrence of isolated slow spiking. Both were placed on Dilantin and Thorazine with clinical improvement.

The next illustrative case is that of a 13 year old girl who came to us three months after the occurrence of her first grand mal seizure. Of interest is the fact, however, that since early in ner life she has had Jacksonian attacks involving the right eye and eyelid, and her grand mal convulsions are heralded by a lateral deviation of the right eye and spasm of periorbital muscles on the right. She also had complained since early talking days of a right hemicranial headache, sudden in onset, throbbing and intense, of irregular occurrence, and previously diagnosed as a migraine type. Her electroencephalographic tracing was grossly abnormal, with the occurrence of marked slowing in the frontal leads.

Her grandfather had similar headaches, no seizures. Her father is 56, is an obsessive, rigid type individual who has suffered headaches since his early teens, and has a typical migraine headache involving first the right hemicranium, with spread to the entire cranium and accompanied by optic symptoms. This man has a history of on two occasions having had outbursts of violent temper, during one of which the life of another individual was threatened. He has amnesia for these attacks, and he reports himself as having, characteristically, a violent temper. His electroencephalogram shows irregular frontal lobe lead abnormalities in the form of isolated slowing of higher amplitude than his regular rhythm.

B. P. is a white male, age 16, who came to the office complaining of chronic morning headaches and occasional blackouts. The blackouts are ushered in with diplopia, which is followed by a short period of unconsciousness. He relates the headaches to his blackouts in that he feels that his lapses are an extension of a severe headache. His electroencephalogram shows bursts of higher than normal voltage and the occurrence of some slow spikes. Of especial interest, here, is that the mother suffers no disturbance of consciousness but was diagnosed early in life as having migraine headaches, as were also her grandmother and her father. She was 43 at the time her tracing was made and her electroencephalogram shows isolated short bursts of slowing very similar to those seen in her child.

Mrs. R. E. G., a 45 year old white female suffered headaches with her menses as a teen-ager, with progression of this symptom to a migraine-type syndrome diagnosed as such several years ago. She was more recently subject also to attacks of ictal emotion, sometimes in the form of outbursts of anger, and at other times she would become wildly hysterical and apparently disoriented. It was of especial interest to us in this case that at rest and with hyperventilation she had what we would consider a normal electroencephalogram. However, with photic stimulation there was a decided buildup in voltage and the occurrence of irregular but sustained slowing, and at some frequencies she appeared to assume the rhythm of the photic stimulator. Her abnormality was most marked at frequencies of 10-11 flashes per second. Her symptoms were dramatically controlled with Dilantin and Thorazine.

Mrs. N. T. is a 25 year old white female who suffered with attacks of feelings of inability to swallow followed by feelings of panic, with acute anxiety, desperation, and violent shaking and jerking involving all limbs, and who remained conscious during each episode. She has a life-long history of asthma and of violent headaches suffered as a child prior to the onset of menstrual flow. There is evidence of cerebral trauma at birth. The family history in this instance is negative. The electroencephalogram is obviously abnormal, with bursts, of a few waves in duration, of high voltage slowing. Her family doctor reports dramatic improvement after she was placed on medication of Dilantin and Thorazine.

C. E. is a 16 year old white male whose father has paroxysmal outbursts of violent temper, and who by description is a rigid, obsessive-type individual. The child began with recurrent, increasingly severe headaches as he entered adolescence, and these became increasingly severe headaches as he entered adolescence, and these became increasingly severe to the point of hospitalization and the use of narcotics to control pain. It was at this point that we saw him. His electroencephalogram reveals slow spike formations occurring at random and a tendency toward disorganization. There was no obvious response to psychotherapy or to Thorazine given in relatively high doses, with a rather dramatic cessation of his recurrent headaches when Dilantin was added to his medication.

Mrs. L. T., is a 36 year old white female who came

to us with a history of 6 years duration of severe migrainoid paroxysmal-type headaches which were especially severe during her one pregnancy. These attacks were heralded by an aura of a feeling of light-headedness or dizziness and extremes of photophobia. She had an occasional brief fainting attack which she had not before mentioned to her doctors because she felt these to be an extension of the wooziness or dizziness at times experienced as the aura of her headache. The fainting had been in existence for only about a year. She had had some 5 attacks but they were short-lived. For instance, she had one while driving and recovered consciousness before leaving the road. Her family history includes convulsions on the part of the mother, who had them as a small girl, and who also suffered with migraine type headaches occurring with her menses. Both reportedly have what they call a hot temper, which actually consists of attacks of anger during which there is loss of control and environmental contact for a short time. Her electroencephalogram showed only a slight abnormality. This was apparent to some extent with hyperventilation but much more marked with photic stimulation, and consisting of some increase in amplitude and a tendency toward slowing seen in all leads. This patient reported marked improvement with Dilantin without the use of Thorazine.

E. K. is a 5 year old boy who was first diagnosed as having a chronic convulsive disorder in 1953 on the basis of a history of overt gross seizures of grand mal and petit mal types, with an abnormal electroencephalographic tracing at the time. Prior to the onset of overt convulsions, he complained frequently of headaches which would stop his play. The child is also a behavior problem and the mother reports severe and frequent temper tantrums since very early in his life. His electroencephalographic tracing is very grossly abnormal, and during the tracing he had one typical 13 second burst of slowing to 2 cps, with some spike and dome formation. There is also some random slowing in isolated waves with a rhythm of 3-5 cps, and a marked asymmyetry, the right temporal and occipital leads were of constantly higher voltage than the rest of the record. Although there was an occasional occurrence of convulsions, there was a relief of temper tantrums and headaches with the addition of Thorazine to his anticonvulstants.

G. D., a 26 year old white female, had recurrent attacks of hostile, temper ridden, behavior of 6 years' duration. She has an aura of what she calls a "strange feeling in the head," and her husband can predict attacks by a "strange look". The attacks last 2-3 minutes. Interestingly, the patient had often in the past gone to the police to be confined to avoid the consequences of her wild actions during a "spell." Also, she complained of severe and debilitating, generalized headaches. Her electroencephalogram is abnormally fast with frequent paroxysmal short bursts of spiking type waves. There was considerable symptomatic improvement on Dilantin and Thorazine, and to our knowledge she had not been in jail since medication was begun.

D. M., a 48 year old white male described his chief complaint as "Spells when I get wild and I have to fight," and a chronic, frontal, low grade headache. The spells at times are stopped or relieved by vomiting. His electroencephalogram was abnormal, with bursts of slowing to 5-6 cps occurring primarily in the parietal leads. There was considerable relief from anticonvulsants and Thorazine.

Mr. and Mrs. H., a young married couple, Mr. H. 30, and Mrs. H. age 29. They came because of domestic difficulties hinging around their mutual outburts of temper. Mrs. H. has the most severe flareups and becomes wildly angry and out of contact for short periods. Her electroencephalographic tracing is abnormal. With hyperventilation she showed bursts of high amplitude and irregular slowing with disorganization. Dilantin and Thorazine were suggested. Mr. H. has outbursts only after a few drinks, but these are violent and he becomes assaultive and abusive. His electroencephalographic tracing is regarded as well within the limits of normal. We did not inject alcohol to measure that effect.

Conclusion

We believe that certain instances of migraine headaches are related to the familial occurrence of cerebral dysrhythmias, though not of any specific type and that a positive family history of ictal emotion and/or headache is useful in the diagnosis of the syndrome, and that this explains in part why they are benefited by Dilantin. All of the patients in the illustrative case histories have been treated with anticonvulsants and/or Thorazine. We have noticed relatively little in the literature about the significance of an abnormal electroencephalogram occurring with headaches. We hope that these cases will contribute, in some small measure to our understanding of this problem. It has been our experience that Dilantin is by far the most adequate in the successful treatment of this type syndrome. Also, of considerable interest is the fact that several of the cases were not controlled by Dilantin alone, but with the addition of Thorazine there has been dramatic improvement. This is also true of cases in which Thorazine was tried alone and dramatic improvement occurred with the addition of anticonvulsants. The dosages which we have used most successfully have been relatively small ones. We usually begin with Dilantin grains 1½ given twice daily with 25 mg. of Thorazine, with dosage regulation as symptomatology dictates.

Evaluation of the Therapeutic Effects of Drugs in Psychiatric Patients

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I. Introduction:

The introduction of the phenothiazine derivatives, chlorpromazine (Thorazine) and promazine (Sparine); the rauwolfia alkaloids; and more recently such drugs as phenyl-piperidylacetate ester (Ritalin), pipadrol (Meratran), azocyclonol (Frenquel) and meprobamate (Miltown, Equanil) has aroused much enthusiasm for pharmacological treatment of psychiatric illness. It can be reasonably expected that during the next few years many drugs with "ataractic," "psychotropic," or other alleged therapeutic properties will become available for clinical trial.

Such trials, depending upon the judgment and skill with which they are carried out, can have various results. Ideally, within the limitations of the descriptive methods currently available, they should offer an accurate account of the behavioral and therapeutic effects of a drug. However, they can and frequently do lead to publication of inaccurate or false results. This gives rise to the almost predictable sequence which in recent years has followed the introduction of drugs of unusual interest or promise. It consists of initial over-enthusiasm, usually based upon a small number of preliminary, optimistic reports; this is followed by disenchantment as subsequent, more systematic studies fail to verify initial claims; eventually an accurate picture of the usefulness and limitations of the drug evolves. Meanwhile, there is a long period of false expectations, wasted therapeutic and investigational time, and disillusionment to both patient and physician. This sequence is already evident in the psychiatric field under discussion and presumably will become more conspicuous as the number of available drugs multiplies.

Evaluation of the psychological and behavioral effects of drugs involves one of the key problems in psychiatry, i.e., the creation of reliable methods for observing and recording phenomena which are intrinsically difficult to estimate or even define. However, assuming that methods of reasonable reliability for observing such events can be devised, one must then design the study to ensure confidence that the critical variable, the drug, and not a variety of other possible variables, is the determining factor in the observed change. These intervening variables of drug evaluation are numerous and in many instances subtle and difficult to detect.

Many fine contributions on method and experimental design for drug evaluation are available in the literature. Unfortunately, this information and implied recommendations have not had as much influence upon investigational practices as one would hope. It has also not been as readily accessible, in summarized form, as it might be to the busy physician or psychiatrist who, in the final analysis, must critically review available data on therapeutic effects to decide upon the most useful agent.

It is the purpose of this paper to summarize a number of the more frequently used methods of drug evaluation, with comments on their relative value and to review possible sources of error in their use. An effort has been made to organize the material in a readily accessible and schematic form. Many comments will be self-evident to the reader in terms of common sense and his basic knowledge of scientific method.

II. General Comments:

The kinds of data with which we are concerned consist of the following: (1) verbal accounts by the subject as to his state of mind, given either spontaneously or in response to inquiry; (2) verbal and behavioral response of the subject to standardized verbal or symbolic stimuli (e.g., psychometric tests) or to structured performance problems or social situations; (3) inferences by observers about the significance of verbalizations and behavior, particularly as evidence

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of degree of mental disturbance; (4) observations of the routine behavior of the subjects in terms of capacity for self-care, work performance, interpersonal relationships, and social problem solving, and inferences therefrom as regards degree of mental disturbance.

Conclusions as to therapeutic effects must therefore depend upon communicational data and observations of individual and interpersonal behavior. These will always represent a complex resultant of several factors. They consist of the neurophysiological effects of the given drug (and concomitant representation in awareness), of their effects in turn upon the functioning personality in all its perceptive, integrative, and executive aspects and rich individuality, and finally of the physical and interpersonal environment insofar as it facilitates or limits expression of this altered mental state. These are invariable parameters conditioning the type of behavior with which we are concerned as psychiatric observers. Such parameters of personality and environment are of course not relevant in the case of drugs which in adequate dosage would predictably produce, for example, general anesthesia or convulsive seizures in all individuals. They are of considerable importance, however, for drugs affecting behavior in its conscious, adaptative aspects, as in treating psychotic patients.

It is obviously important for investigators to define standards of "therapeutic" response or "improvement." Such standards have both quantitative and qualitative aspects. Statements that patients showed "no improvement," "slight improvement," or were "much improved" have little meaning unless information is given about the criteria of improvement used and the means by which these were rated. These standards would be met in elementary form, for example, if an indication of mental illness such as hallucinations were reported as present or absent on the basis of specified observations. With more elaborate methods such as rating scales, the specific items of behavior sampled can be numerically rated at appropriate intervals and the significance of the changes in the ratings evaluated by statistical means.

There is another reason for specifying the nature of the improvement obtained in mental patients. It is well known that patients can remain grossly psychotic and yet become passively cooperative, less overactive and destructive, or more docile. These changes can be achieved by intensive activity programs or a variety of other means. Such improvement may be more important to the custodian than the patient. On the other hand, evidence of resolution of the psychotic process, reconstitution of non-psychotic defenses, or significant degrees of social re-integration would represent improvement of very different significance.

III. Sources of Error and Their Control:

A. *In the observers:*

(a) Regardless of their conscious good intentions or intellectual honesty, investigators are subject to bias when observing patients treated with a drug from which therapeutic or other psychological effects are anticipated. There is wide latitude for selective attention or inattention to the many facets of behavior available to our inexact methods of observation. The choice of events observed and recorded and the repression of others may be subtly affected by the investigator's unconscious needs for achievement. Other observers or raters, depending upon their feelings toward the principal investigator, may unconsciously please or, more rarely, displease him by their observations on the treated patients. These are only a few of the many possible sources of bias. They can be controlled only by use of a design which "blinds" observers or raters as regards the drug-treated subjects. This may be difficult to achieve. Raters may expend much effort to overcome the "blinding" because of their pride in uncovering drug effects, or resolve their curiosity about such effects by extracurricular study of available periodicals. The investigator may be quite unaware of these activities.

This becomes more of a problem if the drug being studied has been previously reported or if the drug-treated subjects can be readily identified among the placebo controls by the occurrence of conspicuous subjective or side effects. An inert placebo may be unsatisfactory under these circumstances; it may be preferable to use a known drug which mimicks these effects.

(b) There is another less apparent source of error. As an interviewer or rater sees patients on repeated occasions over an extended period, making comparisons between present and past behavior, he may note more evidences of self-help, social skill, rewarding interpersonal behavior, etc., and describe them as improvement. Actually, it may turn out that these features were previously present but not observed. In large institutions with limited staff there is a tendency to think of patients as stereotypes, or perhaps caricatures, with certain conspicuous features of the individual determining one's way of thinking of him. This may markedly condition the initial behavioral ratings. Introduction of a drug study into such a setting intensifies observation and focus upon individual behavior. Increasing awareness of the details or resourcefulness of a patient's ward adjustment may be recorded as improvement. This source of error can only be controlled by the use of an adequate baseline control period during which ratings or observations become stabilized.

(c) Whether one is using standardized interview or behavioral rating scale methods, certain preliminary steps are important. The observers should be trained in the method employed. Their reliability or standard error on successive ratings on an adequate number of stabilized subjects at adequate intervals of time should be determined. Multiple, independent raters or interviewers are desirable and inter-rater comparisons on the same subjects should be carried out. Markedly deviant raters should be withdrawn. Such raters or interviewers may be found, for example, to be reacting with halo effect to some facet of the patient's behavior to which they are personally sensitive.

B. *In the patients:*

(a) "Spontaneous" variations in the course of the psychiatric illness and "spontaneous" improvement may be very appreciable sources of error, particularly in evaluation of the treatment of patients with acute schizophrenia or affective psychoses. The longer the duration of the drug therapy, the more of a problem such errors become. An adequate number of cases must be treated and the results compared with a comparably managed control group. Some of the difficulty can be avoided by drug trials on chronic, stabilized psychotic patients.

(b) The number of cases to be used for drug-treated and control groups and the choice of methods by which they are selected are critical decisions in a drug study. The statistical and other considerations involved in this problem cannot be discussed in this paper. It is obvious that treated and control groups should be as comparable as possible. If matched groups are used, the prognostic or other criteria used for matching should be specified.

(c) It is well known that individuals may differ widely in sensitivity to equal amounts of the same drug. This fact should be considered in a drug study. The results from treating a group of patients with a standard dose may be quite different from those obtained when dosage has been pushed to some level of "tolerance," "toxicity," or other individualized end point. The body weight of the patient also affects dosage response. The effects of a given amount of drug will be obviously different when given to a hundred pound person as opposed to one who may weigh twice as much. Reporting dosages as mgm./kgm. would help in this regard.

(d) Intervening variables may affect patient behavior during a drug study as follows:

(1) A new medication, especially if accompanied by enthusiasm and optimism on the part of the staff, may in itself have beneficial effects upon behavior. However, these suggestive effects are generally limited in extent and short in duration. They can be controlled by a placebo group and adequate length of drug trial. The patients of course should be "blind" as to the nature or anticipated effects of the drug being given.

(2) Failure to hold the ward environment constant, both physically and in terms of personnel, may introduce intervening variables. These include changes in activity programs as well as addition or withdrawal of personnel or changes in their quality. The introduction of rehabilitation efforts in the course of a drug study, as improvement makes these more feasible, will of course exaggerate apparent drug effects.

(3) Significant improvement in therapeutic climate may be a side effect of the introduction of a drug study. This is particularly true of "back wards" or other settings which have previously been therapeutically inactive, or where available therapeutic methods have not achieved significant gains for long periods. There may be increased interest and enthusiasm on the part of the physicians and improved morale and motivation among nurses and aides. These attitudinal changes may be reflected in more active participation and interpersonal exchange with patients and an assumption that there is greater potential for rehabilitation than before. Of course, such potential may have previously existed. If there is a "blind" control group, it may share these effects and move behaviorally closer to the drug group to the extent of their influence.

(4) Another, less apparent, intervening variable can arise from the drug-induced or "spontaneous" improvement of several patients involved in a drug study on a ward. If such improvement is appreciable, especially if it brings increased social integration, these patients can significantly increase the availability of rewarding social contacts or otherwise stimulate the non-responders to the drug as well as the control group. The "atmosphere" of the ward becomes generally better. This sequence would not be undesirable from a therapeutic standpoint. From an investigational standpoint, however, it can lead to overestimation of drug effects by stimulation of non-responders and underestimation by improving the functioning level of the control group.

IV. Methods of Drug Study: Their Advantages and Limitations:

A. *Interview Methods:*

These methods depend primarily upon introspective reports from the patient, but specific aspects of such information can be elicited by inquiry and additional information inferred from the subject's behavior in the interview situation. Many refinements have been made in such methods to control sources of error in both subject and observer. These refinements include:

(1) Double-blind techniques to conceal the nature of the drug given and its anticipated effects from both patient and interviewer.

(2) Use of an adequate number of subjects and controls to minimize individual differences. Controls should receive an appropriate placebo.

(3) The use of standardized interviews in order that the observations may be more precisely repeated by the same interviewers or confirmed by others.

(4) The use of multiple, independent interviewers for each subject in order to control rater bias and differences.

(5) Methods for carrying out systematic, more objective analysis of the interview content.

(6) Introduction of periods of drug and placebo administration, by "doubleblind" methods, into a prolonged series of structured interviews such as are involved in psychoanalytic therapy. The observer-therapist has in this instance a rich knowledge of personality dynamics which may modify drug effects. Only a very limited number of cases can be studied by this intensive, longitudinal method. At the conclusion of the study, an effort is made to correlate data from the therapist's day-to-day notes with the intervals of drug or placebo administration.

With suitable controls and refinements, as outlined above, these basic methods of clinical psychiatry can afford valuable and extensive information about the psychological and therapeutic effects of drugs. The data can be more precise in terms of the psychic mechanisms and interplay of personality forces involved in a drug effect than those obtained by the rating scale methods discussed below. In pilot studies of a new drug, interview methods can be useful to obtain an impression of the aspects of personality function affected by the drug. These can become leads for the choice of appropriate rating scales or other more systematic observational methods.

However, if high standards of reliability and control are required, these methods can become remarkably cumbersome and laborious. The number of skilled interviewers available is frequently small. Moreover, the interview situation samples only a limited portion of the patient's total behavior. One may miss significant changes which occur

during the non-observed portion of the patient's day. In the case of psychotic patients, especially if they are regressed or withdrawn, interviews may be grossly inadequate samples of their behavior.

B. *Evaluation of Drug Effects by Use of Psychological Tests:*

Psychological testing represents essentially a structured interview during which standardized tests involving psychomotor performance are given or standardized verbal or symbolic stimuli are presented to elicit thought processes or projective responses. They have many of the same advantages and disadvantages as interview methods. In general, they have limited value for evaluating the therapeutic effects of drugs in mental illness. Some tests, those measuring psychomotor performance, have good reliability and can be repeated, but they give very limited information. Others, such as the projective tests, afford more extensive psychological information but do not hold up well on repetition and are subject to the same interpretational bias and need for double-blind control as interview techniques.

C. *Evaluation of Drug Effects by Use of Behavioral Rating Scales:*

These methods are extensively used at present. A variety of behavioral rating scales are available or similar scales can be devised for the problem at hand by routine methods of scale design. It is obviously important that the items in the scale correspond to behavior which is presumed to be sensitive to drug-induced change. The necessity of rater training and determination of rater and inter-rater reliability have already been discussed. It is desirable to have multiple, independent raters who sample a reasonably wide range of the patient's daily activity. Improvement as manifested by ratings should have statistical significance when compared with baseline or control ratings.

Rating scale methods make it possible to employ ancillary ward or hospital personnel and to study large groups of patients. They can be well-controlled if the intervening variables are considered and they give rough quantitative results. However, the behavioral information obtained is limited to the items rated. Some aspects of drug-induced behavioral change may be missed by exclusion from the scales. They give limited information by which one can predict a drug response in an individual case.

D. *Evaluation of Drug Effects by Sociometric Methods:*

These methods have been used only to a limited extent for the study of drug effects. They consist essentially of various techniques for carrying out systematic observations on personal and interpersonal behavior in the ward or other setting. Verbal and non-verbal exchanges between patients and patients and staff are recorded. Intervening variables and other sources of error must be controlled and intervals of adequate duration sampled at comparable intervals. Although more difficult to quantitate, such methods can be remarkably sensitive in disclosing the effects of drugs on social integration, problem solving, and other important aspects of interpersonal dynamics which are, of course, critical areas of disability for the psychotic patient.

V. Final Comments:

As was noted in the introductory section, pharmacological treatment of psychiatric illness is a rapidly expanding and promising field. It is likely that an increasing variety of drugs will become available for therapeutic trial. The use of adequate observational methods and an experimental design which controls intervening variables has been described as a necessary condition to ensure accurate drug evaluation. The harm which can accrue from publication of inaccurate or misleading conclusions about therapeutic effects has been emphasized. A critical appraisal of some methods of drug evaluation and sources of error in their use has been made. It is hoped that this information will be of value to physicians and psychiatrists who must make decisions about the validity of therapeutic trials reported to them. In turn, it behooves those reporting drug investigations to describe methods, design, controls, subjects, and circumstances of the study in such a way that critical appraisal of the results and comparison with the results of other studies become possible.

Treatment of Choice in Mania Complicated by Peptic Ulcer

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Psychiatric patients exhibiting as part of their clinical picture both the symptoms of mania and of peptic ulcer are rare but certainly not unknown. A prevalent attitude in certain sectors of psychiatry has been that the presence of a psychosomatic disorder would militate against the occurrence of a psychosis in that the former could be considered defensive. However, the data have not backed up this impression and it seems clear that peptic ulcer and mania may be present at the same time. Thus, Honig[1] in a recent paper reports one case in which ulcer coexisted with manic depressive psychosis and Ross, Hay and McDowall[2] report four cases of peptic ulcer in manic patients. West and Hecker[3] provide figures which indicate that the incidence of peptic ulcer in hospitalized psychotic patients is essentially the same as in the general population.

In light of the above material, the question arises as to whether treatment in the manic patient might be complicated by the presence of an active peptic ulcer. Following is a case report of a patient of this sort in which there is suggestive evidence that the ulcer did indeed interfere with the treatment and give rise to the necessity of altering the regimen for the handling of the patient.

Case Report

W. D. is a 32 year old white male admitted to the psychiatric service of the Barnes Hospital May 10, 1955, presenting a picture of hostility, belligerence and aggressiveness of two weeks' duration.

In January 1955 the patient had become preoccupied with religious matters and attempted to convert his friends in his hometown. He would drive his auto recklessly through the streets of the town, he would talk incessantly and stayed awake until the early morning hours. These symptoms occurred at the time that he was slated to take on more responsibility in his work and was given the task of building up his section of the store in which he worked.

Because of the above symptoms he was taken to a private psychiatric hospital near his home and given 13 electro-convulsive treatments. During the course of ECT he developed abdominal pain, tarry stools and had a recurrence of a large peptic ulcer. The ECT was discontinued. The severe pain seemed temporally related to the treatments. The patients was placed on an ulcer regimen. He was discharged from the hospital to his home approximately two weeks prior to his entering the Barnes Hospital. At this time he was belligerent, struck his wife and child and threatened his father with a gun. He had followed his diet poorly.

Past History. — The patient had been brought up by a compulsive father who constantly depreciated the patient's efforts at anything. The mother has suffered for years from a peptic ulcer and the maternal grandfather died as a direct result of a peptic ulcer. At the age of 15 the patient was sent to a military school and remembers crying a great deal for several days on leaving home. At 18 while at college the patient had peptic ulcer symptoms for the first time followed by perforation. The perforation was closed in surgery. It appears that during this episode he also was quite belligerent and aggressive. The patient had ulcer symptoms about every spring and autumn for the years in between his admission to Barnes and the perforation. He has also had frequent periods of depression accompanied by self-condemnation and somatic preoccupation.

Course in the Hospital and After Discharge.—A GI series done May 20, 1955 one

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day after admission to the Barnes Hospital revealed a duodenal ulcer and as a result antispasmodics (probanthine) and antacids were immediately given. The patient was started on 100 mg. of chlorpromazine I.M. and then given 100 mg. by mouth three times a day. By the second week of hospitalization he was getting 1600 mg. chlorpromazine a day in four divided doses. The ulcer pain subsided and the patient's hostility and overactivity decreased. The chlorpromazine was reduced and the patient was discharged on 200 mg. four times a day. At the time of his discharge June 25, 1955, the ulcer was considered healed. The patient continued on chlorpromazine throughout the summer and fall of 1955. He experienced a few days of hyperactivity which were controlled by raising the dosage of chlorpromazine. His gastrointestinal symptoms were minimal and the patient reported them as an occasional feeling of abdominal upset. He felt they were the least in intensity since he had developed the ulcer at the age of 18.

Discussion

There are many factors of this case worthy of discussion. There is evidence that the patient's ulcer symptoms are closely associated with his manic behavior. It would be of interest to know if his mother and maternal grandfather, both of who suffered from peptic ulcer, also were subject to periods of hyperactivity. Unfortunately the material available is not complete and of value only for speculation.

One fact is clear, however, from the history. With the administration of electroconvulsive theray the patient's ulcer symptoms became worse; and added to the obvious hyperactivity was the hostility and belligerence. It is possible to explain the increased ulcer difficulties by consideration of recent research. Bliss, et al.[4] compared the 17 hydroxycorticosteroid levels in plasma before and after electro-convulsive therapy and found that it was significantly higher after treatment. They point out that it is clear that the shock therapies cause an increase in the concentration of adrenal steroids in the circulation which in turn has an effect on the cells of the body. Gray et al.[5] present data indicating that the administration of adrenocorticotrophic hormone produces an increase in gastric HCl secretion which is correlated with peptic ulcer symptoms and ulcer pathology. They conclude that there are significant hormonal influences in addition to the neural stimuli through the vagus nerves in the pathogenesis of peptic ulcer. Considering the above two pieces of research, a rationale is available for the effect of ECT on the patient's peptic ulcer and one would not be remiss in suggesting that the administration of ECT in neurosis or any psychosis with peptic ulcer is unwise if there is another type of therapy available.

It may be noted from the case protocol that the patient responded rather well to the usage of chlorpromazine. The efficacious effect of chlorpromazine on attacks of psychomotor excitement seems generally accepted and has already been reported in the literature by Lehman and Hanrahan.[6] It is of some interest, however, that the patient believed he had less difficulty from his ulcer after his discharge from the hospital than he had had for many years. This period of relative comfort coincided with his taking a high dosage of chlorpromazine. One of the questions which would then arise is whether the drug in any way influenced the levels of corticoids in the blood or had an effect on the neural stimuli to the gastrointestinal tract.

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Treatment of Anxious Patients With Drugs

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Anxiety, in one form or another, is the most common symptom confronting the practicing physician. It has been estimated that one-third of all patients seeking medical assistance suffers primarily from some manifestation of anxiety and that as many more have anxiety secondary to some other medical problem.[1] The best treatment for anxiety is to remove its cause, whether psychological or medical. Frequently, it is desirable to attain some degree of symptomatic relief of anxiety before definitive treatment is undertaken. Symptomatic relief may be all that is ever feasible for some patients.

Sedative drugs have been widely used for symptomatic relief of anxious patients in the past. Until recently, phenobarbital has been the favorite drug of this type, with prescriptions containing barbiturates near the head of the list of prescribed drugs.[2] Because of its concomitant hypnotic properties, phenobarbital has not been an ideal sedative despite its great popularity. The recent introduction of "tranquilizing" or "ataractic" drugs has broadened considerably the choice of agents producing symptomatic relief in anxious patients.

Methods and Materials

A total of 131 hospitalized psychiatric patients were studied. The diagnoses were psychoneurosis in 103 patients (90 of whom had anxiety reactions), schizophrenic reaction of the pseudo-neurotic type with no disorganization of personality or distortion of reality in 17, personality disorder (chiefly emotional instability reaction) in eight, and other diagnoses in three patients. All patients had anxiety as the predominant symptom. The patients were men, most of them veterans of World War II. Their ages ranged between 21 and 64 years, the median age being 32 years. The psychiatric disorder had been present for periods varying between two and twelve years, the median duration of illness being eight years.

The aim of these studies was not primarily to assess the long-term usefulness of drugs in treating anxious patients, but to determine their efficacy in providing symptomatic relief and facilitating the definitive treatment. The double-blind method was used in four trials involving 97 patients. These trials were conducted as follows:

1) Twenty patients received alternate 21 day courses of reserpine 1.5 mg. daily or placebos identical in appearance. The patients were not aware that two separate courses were being given consecutively and the physicians did not know the order of administration of the drugs.

2) Twenty-five patients received alternate 21 day courses of reserpine 1.5 mg. daily or phenobarbital 90 mg. daily. The two drugs were offered in similar tablets, using the same technique described above.

3) Twenty-eight patients received alternate 21 day courses of the alseroxylon fraction of Rauwolfia serpentina 12 mg. daily or placebos.

4) Twenty-four patients received alternate 21 day courses of meprobamate 3200 mg. daily or placebos.

All patients in the double-blind trials were later maintained or started on active drugs for continued treatment. Twenty patients, all of whom had previously received reserpine, were given equivalent doses (1 to 1.5 mg. daily) of another pure alkaloid of Rauwolfia, rescinnamine. Fourteen patients, all with severe degrees of anxiety, were treated with chlorpromazine daily doses of 200 to 800 mg.

Judgment of improvement was made on the basis of what the patients said and did. Prior to treatment each patient was interviewed regarding his symptoms. A feeling of inner tension, restlessness, insomnia, headache, and lack of appetite were frequently mentioned. These initial symptoms were compared with those described at subsequent interviews during the course of treatment. In addition, each patient was un-

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der close observation during the trial of therapy. He was judged on the basis of his cooperation in ward routine, his ability to relate with personnel and other patients, his accessibility to psychotherapy, and his described behavior on passes or leaves from the hospital. No patient was rated as having improved unless both he and the ward staff agreed that improvement had occurred. If a difference was noted between the courses of treatment, the degree of change must have been unequivocal. Because of the short period of the double-blind trials, improvement was sometimes slight, even though definite.

Results of Studies

1) Reserpine 1.5 mg. Daily Compared with Placebos: 20 Patients.

Nine patients experienced symptomatic relief coinciding with the administration of reserpine. Two patients improved on placebo only. Four patients improved on both reserpine and placebo, while five were unchanged during the entire trial. (Table 1.) Complaints of fatigue, irritability and mental depression, tremulousness, and nasal stuffiness were frequent in these patients. Although some of these complaints were also reported during periods of placebo administration, the difference in frequency of side reactions was significantly higher in patients who were receiving active drug.

TABLE 1

Reserpine 1.5 Mg. Daily Compared with Placebos in Twenty Anxious Patients

	Number Treated	Improved on Reserpine	Improved on Placebo	Improved on Both	Unchanged
Anxiety Reaction	15	8	1	2	4
Psychoneurosis, Other	1	0	0	1	0
Schizophrenic Reaction	3	1	1	0	1
Personality Disorder	1	0	0	1	0

2) Reserpine 1.5 mg. Daily Compared with Phenobarbital 90 mg. Daily: 25 Patients.

Fourteen patients experienced symptomatic relief coinciding with the period in which reserpine was given. Two patients improved on phenobarbital and felt worse on reserpine. Four patients improved equally on both drugs, while five showed no appreciable change during treatment. (Table 2.) Judging by the reactions of patients during the two phases of treatment, reserpine increased their ability to deal with their emotional problems. The main effect of phenobarbital was to induce better sleep. Side reactions were greater from reserpine than from phenobarbital.

TABLE 2

Reserpine 1.5 Mg. Daily Compared with Phenobarbital 90 Mg. Daily in Twenty-five Anxious Patients.

	Number Treated	Improved on Reserpine	Improved on Phenobarbital	Improved on Both	Unchanged
Anxiety Reaction	15	7	2	3	3
Psychoneurosis, Other	4	3	0	1	0
Schizophrenic Reaction	3	2	0	0	1
Personality Disorder	1	0	0	0	1
CBS*, Trauma	2	2	0	0	0

*CBS—Chronic Brain Syndrome

3) Alseroxylon Fraction of Rauwolfia 12 mg. Daily Compared with Placebos: 28 Patients.

Fourteen patients experienced symptomatic relief during the course of active drug. Two patients improved on placebo more than active drug. Two patients improved both on drug and placebo, while 10 patients showed no significant change during either course. (Table 3.) The side reactions from treatment with alseroxylon fraction were comparable in type to those produced by reserpine though of less frequency and severity. This lower incidence of side reactions was not dependent upon any lessening of sedative effect.

Nine patients had diastolic blood pressures of 100 mm. Hg. or more at the beginning of these trials. Measurements of blood pressure were compared during each course of treatment. Two patients had no significant change in blood pressure after either course. Seven patients had a fall of 15-20 mm. in the diastolic pressure after the course of alseroxylon as compared to placebo. In this regard, alseroxylon fraction produced more consistent lowering of elevated blood pressure than did reserpine.

TABLE 3

Alseroxylon Fraction of Rauwolfia 12 Mg. Daily Compared with Placebos in Twenty-eight Anxious Patients.

	Number Treated	Improved on Alseroxylon Fraction	Improved on Placebo	Improved on Both	Unchanged
Anxiety Reaction	19	12	1	1	5
Schizophrenic Reaction	5	0	1	1	3
Personality Disorder	4	2	0	0	2

4) Meprobamate 3200 mg. Daily Compared with Placebos: 24 Patients.

Eleven patients experienced symptomatic improvement coinciding with the period in which active drug was administered. Three patients improved only on placebo. Three patients were improved by both drug and placebo, while seven patients remained unchanged during the trial of therapy. (Table 4.) Few side reactions were noted from this drug. Symptoms such as dizziness or sleepiness were generally due to overdosage and easily relieved by reducing the dose of drug. A number of patients complained of poor appetite or nausea following use of the drug. Most patients slept well while on meprobamate, something not nearly so often reported by patients on Rauwolfia compounds.

TABLE 4

Meprobamate 3200 Mg. Daily Compared with Placebos in Twenty-four Anxious Patients

	Number Treated	Improved on Meprobamate	Improved on Placebo	Improved on Both	Unchanged
Anxiety Reaction	16	9	1	3	3
Psychoneurosis, Other	3	1	1	0	1
Schizophrenic Reaction	4	1	0	0	3
Involutional Reaction	1	0	1	0	0

5) Rescinnamine 1 to 1.5 mg. Daily: 20 Patients.

Twenty patients who had received reserpine before were treated with rescinnamine, a pure alkaloid of Rauwolfia with pharmacologic properties similar to reserpine. Ten of 15 patients with anxiety reactions were improved by treatment with rescinnamine in daily doses of 1 to 1.5 mg. for 28 days to 140 days. One of two patients with schizophrenic reactions and one of two patients with personality disorder were also improved. One patient with a neurotic depressive reaction was not relieved. Thus 12 of 20 patients treated with rescinnamine experienced symptomatic improvement.

Although the degree of improvement and its frequency were no greater from this alkaloid than from reserpine, rescinnamine produced less side reaction. Because of this, rescinnamine was preferred to reserpine by almost all the patients in this trial. Although a double-blind control was not used, it was felt that these reports of diminished side reactions were reliable.

6) Chlorpromazine 200-800 mg. Daily: 14 Patients.

Patients selected for treatment with chlorpromazine were those in whom anxiety was generally marked by much psychomotor activity and those whom treatment with other drugs in low doses had failed to relieve. The dose of chlorpromazine used in these patients varied between 200 and 800 mg. daily, most of them receiving 400 mg. orally. Seven of 10 patients with anxiety reactions experienced adequate relief of symptoms, as did two of three patients with conversion reactions and one patient with an obsessive-compulsive reaction. Thus, 10 of 14 patients treated with chlorpromazine were improved. Symptomatic relief was often quite rapid, and the patient could be maintained on lower doses thereafter. No complications were noted from this treatment. When doses higher than 400 mg. daily were used, patients were considerably sedated.

Discussion

The physician confronted with the problem of treating an anxious patient now has a larger armamentarium of drugs than ever before. Judging by the results of the various double-blind trials, reserpine, alseroxylon fraction of Rauwolfia, and meprobamate are effective sedatives. Reserpine is more effective than phenobarbital in the doses ordinarily used. Other double-blind trials using reserpine in smaller doses,[3] and a combination of reserpine and chlorpromazine,[4] have been equally convincing regarding the efficacy of these drugs as sedatives. Out-patient treatment of psychoneurotic patients has been highly successful using reserpine in similar doses.[5,6] Alseroxylon fraction, which contains reserpine as well as several other pharmacologically active alkaloids of Rauwolfia, should be expected to be equally effective as a sedative. Meprobamate has been highly effective in treating anxious patients even in lower doses than used in this study.[7,8] Clinical trials of rescinnamine for treatment of hypertension have raised the possibility that this alkaloid might produce less adverse mental symptoms.[9] Despite our uncontrolled trial of this drug, the conclusion appears to be justified that rescinnamine has the same order of sedative effect as reserpine. Chlorpromazine has been extensively studied in treating the major psychoses, but reports are less often made concerning its use in the anxious patient. A favorable report was made using relatively small doses,[10] but other investigators have tended to use higher doses for optimal effects.[11,12]

Side reactions are not of critical importance for hospitalized patients, but among out-patients they may interfere with normal

function. Both reserpine and chlorpromazine produce minor side reactions frequently enough to limit their usefulness in out-patients. Serious side reactions from chlorpromazine (jaundice, leucopenia, and hypotensive crises) are infrequent but present enough risk to limit use of this drug to patients with severe and intractable symptoms. The alseroxylon fraction of Rauwolfia, rescinnamine, and meprobamate have less tendency to produce annoying side reactions and may be more acceptable to some patients. Meprobamate would appear to be the drug most easily tolerated.

No attempt was made in these studies to limit other forms of treatment. To some extent, the lack of such an attempt may have influenced favorably the results, but it reflects our thinking that the drugs play only an adjunctive role. On the other hand, the chronicity of illness, the factor of compensation, and the secondary gains of hospitalization were conditions which made treatment more difficult. Most of the patients who responded well to the drugs early in the course of treatment continued to obtain relief as long as the drugs were continued. A number of patients showed no improvement until a longer course of drug therapy was given following completion of the double-blind trial. As soon as it was felt that the patients were well established in effective psychotherapy, an attempt was made to wean them from these drugs. Some patients exhibited a prompt recrudescence of symptoms when the drug was stopped, suggesting that adequate definitive treatment had not been given. None of these patients had a serious exacerbation of anxiety or depression from the Rauwolfia compounds despite the fact that irritability and depression were changes in mood sometimes produced by the drugs. The reports of exacerbation of mental symptoms in some patients on Rauwolfia compounds indicates that these patients should be closely observed during treatment.[13,14]

Summary

Studies of small groups of patients using a double-blind control were used to evaluate the symptomatic relief of anxiety produced by reserpine, reserpine compared to phenobarbital, alseroxylon fraction of Rauwolfia, and meprobamate. Each of the 97 patients in these studies acted as his own control. In addition, 20 patients were treated directly with rescinnamine and 14 patients with chlorpromazine. Each of the drugs provided effective relief of symptoms of anxiety in one-half or more of the patients treated. Reserpine, alseroxylon fraction, and meprobamate were superior to placebos, and reserpine was superior to phenobarbital in the double-blind trials. Rescinnamine had sedative properties comparable to reserpine. Chlorpromazine produced excellent results when given in large doses to patients with marked symptoms.

The occurrence of minor side reactions limits the usefulness of reserpine in anxious patients. Alseroxylon fraction and rescinnamine produced less troublesome reactions. Meprobamate, because of its relative lack of side reactions and its effective sedation, was judged to be most generally useful in these patients. Because of the rare occurrence of serious complications from the use of chlorpromazine, this drug should be reserved for the most anxious patients, where high doses of drug would be desirable.

Acknowledgment: Reserpine, alseroxylon fraction (rauwiloid), and rescinnamine were supplied by Riker Laboratories, Inc., Los Angeles. Meprobamate (Miltown) was supplied by Wallace Laboratories, New Brunswick, N. J. Chlorpromazine (Thorazine) was supplied by Smith, Kline and French Laboratories, Philadelphia.

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A Rule of Thumb for Evaluation of the "Psychic Age-Group"

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> Men occasionally stumble over the truth, but most of them pick themselves up and hurry off as if nothing had happened.
> *Winston Churchill.*

A middle-aged patient, a successful architect with "new ideas," made a pertinent observation during one of his depressed moods: "Recently I've observed in myself a trait which I dislike. I examine the faces of my collaborators, and even the faces of strangers; I study their facial lines and expressions, trying to figure out how *they* came to terms with *their* disappointments. This mixture of curiosity and resigned gloating is new. It seems I'm getting old." Then, in accordance with the Churchillian observation quoted above, he dropped the topic and reverted to his standard theme of complaints about his dreary fate as an innovator: first ignored, then attacked, eventually plagiarized.

The man's observation, though it was quickly suppressed and subsequently repressed, hit a point of sensitivity common to all middle-agers. Regardless of relative success, he partially accepts his subjectively felt defeat, while at the same time uneasily comparing his state with that of each contemporary. The envious question of youth—"what has the other fellow achieved?"—is now reformulated, and becomes—"how does the other fellow come to terms with and digest his disappointments?" In a few short years, the query will be reformulated into "how long will the other fellow live?"

Youth, middle age, old age, are well circumscribed by these questions. The classification is not necessarily determined by the birth certificate; there are youthful and old "middle-agers," youthful and old "old-agers." The questions these people ask themselves are a reliable clue to their *inner evaluation of themselves*, and therefore provide an answer to the enigma of the "psychic age-group."

It is easy to dismiss this problem with the old wisecrack: "A woman is as old as she looks, and a man as old as he feels." The subjective feeling, the objective appearance, are equally faulty indicators of the *inner* state of affairs. The successive reformulations of a single question listed above, are more accurate indications, especially since most of the individuals observed have no conscious awareness of the meaning or implication of the question. It is most unusual for a patient to make a comment such as that made by the architect quoted at the beginning of this paper. In fact, the architect's feat was so exceptional that he promptly "forgot" his conclusion.

Generally, it is up to the observer alone to register and evaluate the questions people in different age-groups are asking.

What it practically amounts to is an increased deposit of a psychic ingredient most people scoff at, or are totally ignorant of—

psychic masochism. Middle age reminds people of their approaching end. In a spurt of rebellion, they want to begin life anew, only to discover that the irretrievable is irretrievable still. Nearly all men go through a "middle-age revolt," as described in my recent book, "The Revolt of the Middle-aged Man (A. A. Wyn, Inc., New York, 1954.) This "revolt" pertains mostly to the sexual sphere: grandiose plans of divorcing the wife, exchanging the latter for a younger companion, are concocted. Usually these plans come to nothing, or involve the victim of "second adolescence" in greater trouble. Parallel with this trend goes another: the wish to get rid of all obligations, professional and conventional duties.

After a short period (sometimes the whole upheaval amounts to no more than a storm in a cocktail shaker, or to talk, self-torturing thoughts and abortive reactions), the stage of resignation sets in. Before accepting facts as they are, the ominous question is posed time and again: "How does the other fellow digest his disappointments?" Naturally the question contains a good deal of gloating, and is not asked out of curiosity. Every cry-baby look, every depressed expression, every comparatively deep facial fold on the other person's face is taken as proof positive that he too, has found himself in a miserable position.

Is this an indication that malice increases with age? I don't think so. I believe that the ego has become less capable of fooling itself, is more helpless against inner reproaches, and therefore more masochistic. To counteract masochism, pseudo-aggression is emphasized as inner defense. The process continues even more markedly if possible, as the individual progresses toward old age.

What about middle-aged and old men who retain a good many of their previous hopes, aspirations, day dreams and especially, activities? Here an unconscious mechanism of denial and scotomization of facts is observable. The mechanism takes its toll however, in premature organic diseases e.g., heart, or else, in terms of the individual's impact on his environment: he may make himself ridiculous by failing to "be his age." These old men who act like youngsters find it difficult to overcome the unavoidable irony of their juniors. It is true that youth is merciless, and takes advantage of even harmless failings. Boswell records this statement of Samuel Johnson:

> "There is a wicked inclination in most people to suppose an old man decayed in his intellect. If a younger or middle-aged man, when leaving a company, does not recollect where he laid his hat, it is nothing; but if the same inattention is discovered in an old man, people will shrug their shoulders, and say, 'His memory is going.' "

Moreover, the young-acting oldsters are especially hurt when confronted with the unwillingness of young people to accept them, officially, as young, while at the same time unofficially making allowances for their real age. Where this benevolence is absent, depressive trends come to the fore. Here is an example: A great artistic performer while in analysis bitterly quoted an observation made by Jose Iturbi: "The only time you realize you have a reputation is when you're not living up to it." The performer was referring to a critical review which alluded to his age, and was exasperated out of proportion to the importance of the incident.

*

The whole problem of the "psychic age-group" contains a series of unclarified facets, especially in connection with external appearances. Some neurotics look older, some younger, than their actual years. The psychic interconnections are by no means fully elucidated, and uniformity is lacking. In the framework of the still unknown, the three crucial questions enumerated in this study, at least hint at the subjective evaluation of the test-subject.

Eastern Psychiatric Research Association Proceedings

DR. CHARLES BUCKMAN, *Chairman*

Newer Drug Therapies

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The use of Thorazine and Serpasil on an experimental basis was started early in the summer of 1954. Naturally, our staff was interested in testing the drugs for themselves and in verifying the glowing accounts published in the literature. Our findings proved most promising and far beyond expectations.

Since January 1, 1955, there has been ever-increasing use of the tranquilizers throughout the hospital. From that date accurate entries of the cases treated were recorded and reported to the Research Department where further statistical studies will be made for a complete evaluation.

From January 1, 1955 to March 1, 1956 a total of 2,916 patients have been treated, of whom, 2,113 received Thorazine and 803 Serpasil. At this time 121 patients are on a convalescent status, being treated with a maintenance dosage of either Thorazine (89) or Serpasil (32). Accurate records of treatment have been kept for further studies and evaluation.

Experience has shown that the average maintenance dose of Thorazine is from 100 to 200 milligrams daily, and of Serpasil 2 to 3 milligrams. It has been deemed advisable to keep these patients on a maintenance dose as they relapse without it. We are not sure how long these drugs should be taken for optimum benefit. At first we thought that two to three months would suffice, but now we find a maintenance dose must be given for six to eight months or longer. In fact we may have to continue this maintenance dose indefinitely.

This regimen poses two important questions: Is it dangerous to keep a patient on Thorazine this length of time? What tests are needed to safeguard the patient? Good therapeutic procedure demands that a preliminary blood count and bilirubin be done before starting treatment and that routine checks be made bi-monthly for the first two or three months of treatment. Careful clinical evaluation and observation is also essential. On an outpatient basis we believe this should be done monthly, which is the practice adopted in this hospital. Fortunately we have had only a .005% incidence of jaundice symptoms in the cases treated which is very low. Two of these cases, both female, developed jaundice from treatment to admission prior to this hospital. The laboratory found definite liver damage in twelve cases where jaundice symptoms were present. Sixteen cases had elevated serum bilirubin values, none of which showed clinical evidence of jaundice. According to our findings the total value of serum bilirubin above 2 milligrams per cent should be indicative of the development of clinical jaundice, although several cases showed a somewhat higher bilirubin value without developing clinical jaundice. The laboratory findings indicate that Thorazine treatment should be stopped at a value of 1 milligram per cent in order to avoid liver damage. If the bilirubin values go down again in subsequent examinations, the treatment may be resumed. All cases have responded favorably without sequela with immediate withdrawal of Thorazine.

After fourteen months of treatment with Serpasil, it has been determined that preliminary laboratory tests and follow-up are not indicated if routine admission tests are within normal ranges.

We are often asked by relatives if the "wonder drugs" are habit forming. The answer is "no." However, both the therapist and the convalescent patient are apprehensive about stopping the maintenance dose when the patient is adjusting well for fear of the consequences. Many of the general practitioners who help us in our follow-up, as well as the physicians in our metropolitan clinics, often stop the drugs without realizing the significance of what is going to occur. There seems to be a reluctance of these groups to carry patients on a continued maintenance dosage.

On the other hand, many patients, as well as their relatives, have repeatedly requested that treatment be stopped because of untoward side effects. These people are assured that these effects lessen as the treatment goes on after sufficient time has elapsed for the therapeutic effect to take place. When the patients have improved mentally they seldom complain of the side effects.

We concur in the findings of others that if after treatment with Thorazine a relapse occurs, it will require larger amounts of the drug and a longer period of therapy before the previous good results are again reached. Ultimately this result is achieved and the original maintenance dosage again holds the patient.

Large quantities of these new drugs should be administered only in a hospital setting. If followed closely complications are rare with little relative danger to the patient.

Further impressions gained are that these two drugs work best in the group of functional psychoses, particularly the disturbed. Thorazine seems to work faster and relapses occur quicker when withdrawn than with Serpasil. Neither seems to help in depression unless there is a physical or psychomotor hyperactivity with anxiety. Occasionally an involutional type will be helped. Not infrequently depression of a severe type occurs in schizophrenia so that the Thorazine has to be stopped.

We also have used the tranquilizers on organic types with favorable results. Serpasil seems to be more beneficial in idiopathic epilepsy. Thorazine is

*Meeting of April 5, 1956 held at Kings Park State Hospital, Kings Park, N. Y.

the drug of choice in grand mal seizures in general paretics, arteriosclerotics and also the mental defectives with this phenomenon. Following lobotomy, both have been used with equally good results but there is no criteria yet as to which one will work, and the choice is up to the clinician. If one drug does not work we try the other, or a combination of the two. A few lobotomy cases under treatment with Thorazine who formerly had no seizures developed grand mal seizures, or have gone into status epilepticus.

The general overall results depend as may be expected on inherent personality and its preservation of regression, coupled with the duration of the illness. Behavior improves with gradual return of interest in surroundings and then slow but steady fading of delusions and hallucinations. This usually requires several months. Patients improving on Serpasil seem to be more outgoing and outspoken and take a more active part in group therapy than those treated with Thorazine.

In summary, the impact of these two products has been tremendous and truly they may be called "wonder drugs." Their effect in the hospital has been far-reaching. The need for maintenance shock, sedation and mechanical restraint has been greatly reduced. There are less accidents, to patients and employees, and a marked reduction in property damage. Personnel in all echelons are enthusiastic about the improved patient care that can be rendered; consequently, morale of employees has been boosted tremendously.

With these new drugs supplementing our armamentarium we have had to increase our capacity to treat the patient as an individual with psychotherapy, group therapy, occupational therapy and recreational program. The patients are once more in touch with reality and are demanding an opportunity to express themselves.

Laboratory Correlation in Use of Tranquilizing Drugs

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Until recently laboratory examinations had no close relationship to the management of non-organic psychoses. In the past few decades various forms of convulsive therapy—insulin shock, electric shock, metrazol, etc., merely required such laboratory examinations as were needed to screen out physical contraindications. Now, however, with the advent of the tranquilizing drugs laboratory coordination with clinical management of so-called functional psychoses is essential.

The tranquilizing drugs constitute a new pharmacologic advance—specific and predominant action on mental functions, with little or infrequent action on the soma. Hitherto, the basic drug armamentarium of the psychiatrist included sedatives and common pharmaceuticals aimed at counteracting systemic disorders such as cardiovascular diseases, respiratory diseases, acute infections and the like. Treatment was directed at these non-mental disorders primarily to counteract or minimize their interfering effects on psychoses. With the current widespread and intensive administration of promising and potent tranquilizing drugs, an age-old principle of pharmacology now applies to psychiatric practice. This is, that the more potent the drug, the more likely will there be unwanted side-effects.

In the Kings Park State Hospital an intensive program of tranquilizing drugs was begun January 1955. As of the end of January 1956, Dr. Haight, the Clinical Director, reports that 1604 mental patients have been given courses of chlorpromazine therapy (Thorazine). An additional 694 cases were given reserpine (Serpasil).

Published reports indicate that there may be minor or transient side effects in chlorpromazine therapy. Attention has been drawn to the infrequent but more serious complications of jaundice and blood dyscrasia. Even in small series in institutions or private practice, the toxic effects on the liver and blood have resulted in occasional fatalities. Careful clinical and laboratory observations to detect early toxicity is now well established practice. Reserpine therapy, widely used for some years in general medicine, particularly as sedation in hypertensive disease, appears to be relatively safe. Nevertheless, precautionary laboratory checks on the 694 cases receiving this drug were carried out for one year. In no case was there any evidence of jaundice. In one or two cases, a mild degree of anemia, possibly coincidental and irrelevant, were observed. There were no other side effects as evidenced by routine pretreatment and intratreatment laboratory studies.

Laboratory tests were chiefly serum bilirubin and alkaline phosphatase determinations for detecting liver damage; complete blood counts to obviate anemias or agranulocytosis. A routine screening examination was done on all patients in the week prior to instituting therapy. Thereafter, one or more series of blood tests were performed on all patients, beginning in the third or fourth week of treatment and repeated once or twice at monthly intervals. Among 1604 cases on Thorazine treatment, there were uncovered six cases of clinical jaundice with elevated serum bilirubin from 4 to 8 mgm/%, an incidence of less than 4 per 1000. Ten additional patients showed slightly increased serum bilirubin values of 1 to 3 mgm/% without jaundice.

We believe the close attention to laboratory checkups is largely responsible for the low incidence of 4% in this hospital. No blood disorders of a serious nature were found in the entire group although moderate leukopenia was found in several instances. The alkaline phosphatase test was done on a number of patients utilizing the lengthy Bodansky procedure. On two cases, alkaline phosphatase values were high, 16 units and 10 units respectively, with high bilirubin values and clinical jaundice.

Of considerable interest are the recent researches of Goldenberg. Working at the Hillside Hospital,

Jamaica, New York, detailed biochemical studies at weekly intervals, have been conducted on groups of 12 patients on Thorazine. He feels that the alkaline phosphatase test is a more sensitive indication of impraired liver function than serum bilirubin. Liver damage can be detected before there is any laboratory or clinical evidence of jaundice.

Goldenberg points out other significant features of chlorpromazine therapy. First, only a very small percentage of the drug is absorbed by the intestinal tract in oral dosage; the rate of absorption varies widely among patients and is independent of daily amounts administered. In a particular patient, the same constant amount is absorbed entirely whether 100 or 1000 mgm. are ingested. Secondly, the normally functioning liver breaks down 99 per cent of the drug into several compounds with one major compound excreted in the urine as sulphoxide of Thorazine. This intermediate sulphoxide appears to be less toxic to the liver and may be as potent therapeutically. The third avenue of inquiry is the possible parallel between Thorazine blood levels and therapeutic effect analogous to current practice in sulfonamide therapy.

Of laboratory interest is Goldenberg's new vastly simpler chemical method of alkaline phosphatase determination, lending itself more readily to routine surveys in large groups of patients. About 50 to 60 cases are tested each week in the laboratory from an average monthly load of 200 to 250 new cases under treatment. With this spectrophotometric procedure, Goldenberg finds a normal range of 1.5 to 3.9 units of alkaline phosphatase in patients receiving Thorazine; up to 5.5 units are commonly encountered without clinical evidence of toxicity. According to Goldenberg, treatment should be stopped if the values exceed 5.5 units. His own hospital data is necessarily restricted since no more than a dozen cases are treated at one time. Our findings, on almost a thousand patients under treatment, should have greater statistical weight after the phosphatase program is well under way.

Book Reviews

GALEN ON ANATOMICAL PROCEDURES: Translation with introduction and notes by Charles Singer. Cloth. $8.75. Pp. 289. Oxford University Press, 114 Fifth Avenue. New York 11, N. Y. 1956.

Before Galen, Marinus' writings on dissections and anatomy were the chief source of much of Galen's knowledge.

Galen, who flourished during the greater part of the second century, constantly tilted with the Empiric anatomists of his day. For it was the latter who rejected theory and were content to acquire anatomical knowledge solely on the basis of personal surgical experiences. Galen forcefully propounded the dogma that anatomical theory should be included in books on diagnosis, prognosis and treatment as Hippocrates had done before him. Fearing that such strides might perish, he justified the setting down of his lectures in written form "for those who find they need it" . . . (with) nothing but praise for Marinus for recording his anatomical experience, though I (am) myself compelled to write . . . on the same theme, since I have found his both incomplete and obscure."

It is this text of his lectures, presently produced in the English translation from the Greek, that in their Latin translation in the 16th century, had created a profound influence upon the anatomists of the Renaissance period.

For the primitiveness of certain of Galen's false physiological and anatomical concepts, this reviewer would allude to such samplings as that the trachea is a special kind of artery; that the veins arise from the liver and proceed peripherally; that a nerve (neuron), passes into each muscle, then divides and reunites to form the tendon which he also called neuron.

The text in general, is a description of the soft parts of the monkey imposed upon the human skeleton. From numerous passages in the book, when read together, one becomes impressed that Galen was better versed in human anatomy than he cared to set down in writing. Even in our present scientific era, the process of human dissection is usually discussion material relegated o tthe professional atmosphere; and it may well be supposed that this did not differ in Galen's day. A classic passage respecting his structural knowledge of the human anatomy is revelatory and well reflected in his following passage: "If death come to me not too soon, I shall some day explain construction in animals too, dissecting them in detail, just as I have done for man."

The book is practical in that it describes actual procedures of dissection and of physiological experimentation and is unique as the word record of actual lectures delivered by this remarkable teacher who flourished during antiquity. The book makes informative basic reading and furnishes a wealthy contribution to the study upon which the modern revival of anatomy has developed.

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ALCOHOLISM, ITS PSYCHOLOGY AND CURE by Frederick D. Rea, Cloth. Pp. 143. Philosophical Library, Inc., 15 East 40th Street, New York 16, New York, 1956.

This book presents to the lay reader, for whom it seems primarily intended, an accurate and clinicoscopic view of the complexity of the problem of alcoholism. In simple understandable terms, the author assembles basic facts derived from clinical and sociological research into both the causes and the cure of alcoholism.

The early chapters are concerned with definition of the social problem, a description of the metabolism of alcohol, and a discussion of alcoholic addic-

tion with referenuce to the types of individuals and races who are susceptible.

In another section of the book, the various aversion therapies, such as the Shadel treatment, Apomorphine, Antabuse, and medical hypnosis, are described.

The major emphasis of the book occurs in the final chapters. Here the author describes the purposes and activities of Alcoholics Anonymous and states his convictions, based upon four years in that fellowship, that the problem of alcoholism extends across the frontiers of different professions, i.e. medicine, psychiatry, law, and religion. All these disciplines are extorted to unite in order to play a part in helping the individual who suffers from alcoholism. The author believes that there are spiritual or religious deficiencies in the characterological makeup of the alcoholic victim which are as important as some of the psychological, physiological, and sociological factors. Recognition of the spiritual needs of the alcoholic is most important in effecting a cure. Every alcoholic needs a conversion experience, similar psychologically to a religious conversion experience, in order to recover. The healing power of conversion exists in the give and take relationship between the person who offers help and the one who receives it. The helper converts the helped by expression of his willingness to help. In Alcoholics Anonymous, the alcoholic is recognized as having a disease. He is then shown by someone how to accept himself for what he is, namely, a defeated, helpless alcoholic. Then he is encouraged by the example of his Samaritan helper to abstain totally from the use of alcohol. The formula for a successful recovery, then, is acceptance of defeat (self-realization or recognition of the problem), discovery of someone who cares about the patient's problem and is sincerely willing to help, and finally, active and absolute abstinence.

Though the author at times seems too evangelistic in his approach, and though he tends to proselytize the already widely known achievements of Alcoholics Anonymous, he is to be commended for his earnest effort to present a new type of temperance education. Such education is of value to the welfare of the alcoholic. This book is particularly good reading for the family of the alcoholic patient, as well as for doctors, lawyers, psychiatrists, and clergymen.

William W. Zeller, M.D.

THE ROLE OF HUMORAL AGENTS IN NERVOUS ACTIVITY by Bruno Minz, M.D. Charles C. Thomas, Springfield, Ill. $7.75. P. 230.

This monograph was written with the purpose of clarifying the confused ideas about the role of humoral agents in nervous activity. The book begins with an interesting review of the historical aspects of the concept of neurohumoral transmission. Two large sections are devoted to the cholinergic and adrenergic mechanisms. The final chapter is a discussion of the role of humoral agents in the central nervous system.

The literature in this field is voluminous, controversial and confusing. The author reviews and analyzes the large store of experimental and theoretical material and presents in a clear fashion the present status of neurohumoral agents in nervous activity. The analysis seems objective and careful, without prejudice or speculation. He discusses the biological methods used in the studies on a acetylcholine and indicates the advantages, disadvantages and limits of these methods. He points out that so much of the experimental work has been done on animals under most unphysiological conditions and cautions in the interpretation of these results in understanding normal function.

Doctor Minz does not enter into the debate about electrical versus chemical theories of synaptic transmission. He does not maintain that the chemical theory is the correct one, but does list well established humoral phenomena which must be accounted for in any final theory. None of the observed effects constitutes alone an absolute proof of the role of cholinergic elements in the regulation of central activity, although the data furnish a strong argument for that hypothesis. There are indications that other factors, such as thiamine and epinephrine, may be of a certain importance in chemical transmission. Adherents and opponents of neurohumoral transmission agree in admitting that a acetylcholine is somehow involved in nervous activity; they only disagree as to its primary or secondary role. The author points out that the humoral regulation of nervous activity is a very complex mechanism and some of the existing theories are too logical and too exclusive to be entirely valid. He warns that we now know only parts of the very complex problem of synaptic transmission and full understanding must await future scientific research. Unfortunately, no mention is made of serotonin and its role as a neurohumoral agent in nervous activity, but the recent work on this has appeared after the book went to press. There are a considerable number of misspelled words in the book.

Chester F. Cullen, M.D.

BOOKS RECEIVED

A TEXTBOOK OF CLINICAL NEUHOLOGY: By Israel S. Wechler, M.D., Clinical Professor of Neurology, Columbia University, N. Y., Consulting Neurologist, Mt. Sinai Hospital, Montefiore Hospital and Rockland State Hospital, N. Y. Cloth. $9.50. Pp. 801 with 179 figures. W. B. Saunders Company, West Washington Square, Phila., Pa. 1952. New 7th Edition.

PATHOLOGIC PHYSIOLOGY: Edited by William A. Sodeman, M.D., F.A.C.P., Professor of Medicine and Chairman of the Department of Medicine, School of Medicine, University of Missouri, Columbia, Missouri. Cloth. $13.00. Pp. 963, 173 illustrations. Second Edition. W. B. Saunders Company, West Washington Square, Phila., Pa. 1956.

THE PSYCHO-MEDICAL GUIDE: By Curt S. Wachtel, M.D. Cloth. $5.00. Pp. 318. Psycho-Medical Library, 154 Nassau Street, New York 38, N. Y. 1956.

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